

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>6013-118PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/CA 03/01269</b>	International filing date (day/month/year) <b>20/08/2003</b>	(Earliest) Priority Date (day/month/year) <b>20/09/2002</b>
Applicant  <b>UNIVERSITE LAVAL</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

## 1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**METHOD FOR DETERMINING THE PREDISPOSITION OF PATIENTS TO TOXICITY OR LACK OF EFFICACY OF A DRUG**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 03/01269

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,  
no additional fees are to be refunded.

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☒ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

Claims 25- 29 lack clarity (Article 6 PCT) due to the expression "fragment thereof" which does not have any commonly well accepted definition in the art. Moreover the description is silent as regards a definition of said expression, or any length characterising the said fragments. Therefore the search for claims 25-29 has been limited to nucleic acids and molecules having the SEQ. IDs. recited in the claims and the complements thereof.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15, 25 and 26 (all in part), 23 and 24 (in full)

Invention 1 relates to a method for determining the predisposition of patients to toxicity or lack of efficacy of a biologically active compound comprising detecting polymorphism or haplotic variation in UGT1A1 gene wherein the presence of said polymorphism or haplotic variation is indicative of said predisposition.

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2. claims: 1-15, 25 and 26 (all in part), 21 and 22 (in full)

Invention 2 relates to i) a method for determining the predisposition of patients to toxicity or lack of efficacy of a biologically active compound comprising detecting polymorphism or haplotic variation in UGT1A7 gene wherein the presence of said polymorphism or haplotic variation is indicative of said predisposition; and ii) the isolated nucleotide sequence comprising sequences presenting said polymorphism or variation.

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3. claims: 1-15, 25 and 26 (in part), 16-20 and 27-29 (in full)

Invention 3 relates to i) a method for determining the predisposition of patients to toxicity or lack of efficacy of a biologically active compound comprising detecting polymorphism or haplotic variation in UGT1A9 gene wherein the presence of said polymorphism or haplotic variation is indicative of said predisposition; ii) the isolated nucleotide sequence comprising sequences presenting said polymorphism or variation; and iii) the isolated amino acid sequence comprising the translation of said polymorphism or variation.

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## INTERNATIONAL SEARCH REPORT

International Application No

P/A 03/01269

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 C12N9/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 395 481 B1 (RATAIN MARK J ET AL) 28 May 2002 (2002-05-28) examples 1-7; table 1 column 6, line 54 - column 7, line 9 claims 9-26, 43-63	1-15, 23, 24
X	WO 02/48400 A (ANDO YU-UICHI ; SHIMOKATA KAORU (JP); HASEGAWA YOSHINORI (JP); NAGO) 20 June 2002 (2002-06-20) abstract; figure 4 claims 1-31 & EP 1 352 970 A (NAGOYA IND SCIENCE RES I) 15 October 2003 (2003-10-15) ----- -/--	1-15, 23, 24

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

19 March 2004

Date of mailing of the international search report

19.04.04

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## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GAGNE J-F ET AL: "COMMON HUMAN UGT1A POLYMORPHISMS AND THE ALTERED METABOLISM OF IRINOTECAN ACTIVE METABOLITE 7-ETHYL-10-HYDROXYCAMPTOTHECIN (SN-38)" MOLECULAR PHARMACOLOGY, BALTIMORE, MD, US, vol. 62, no. 3, September 2002 (2002-09), pages 608-617, XP009001388 ISSN: 0026-895X Experimental procedures Results Discussion	1-15,23, 24
X	ANDO Y ET AL: "Polymorphisms of UDP-glucuronosyltransferase and pharmacokinetics of irinotecan" THERAPEUTIC DRUG MONITORING, NEW YORK, NY, US, vol. 24, no. 1, February 2002 (2002-02), pages 111-116, XP002967773 ISSN: 0163-4356 the whole document	1-15,23, 24
X	INNOCENTI F ET AL: "PHARMACOGENETICS OF ANTICANCER AGENTS: LESSONS FROM AMONAFIDE AND IRINOTECAN" DRUG METABOLISM AND DISPOSITION, WILLIAMS AND WILKINS., BALTIMORE, MD, US, vol. 29, no. 4, PART 2, April 2001 (2001-04), pages 596-600, XP001008560 ISSN: 0090-9556 the whole document	1-15,23, 24
X	ANDO Y ET AL: "POLYMORPHISMS OF UDP-GLUCURONOSYLTRANSFERASE GENE AND IRINOTECAN TOXICITY: A PHARMACOGENETIC ANALYSIS" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 60, 15 December 2000 (2000-12-15), pages 6921-6926, XP002909302 ISSN: 0008-5472 the whole document	1-15,23, 24
X	ANDO Y ET AL: "UGT1A1 GENOTYPES AND GLUCURONIDATION OF SN-38, THE ACTIVE METABOLITE OF IRINOTECAN" ANNALS OF ONCOLOGY, KLUWER, DORDRECHT, NL, vol. 9, 1998, pages 845-847, XP002909100 ISSN: 0923-7534 the whole document	1-15,23, 24

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## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAMIREZ J ET AL: "IN VITRO CHARACTERIZATION OF HEPATIC FLAVOPIRIDOL METABOLISM USING HUMAN LIVER MICROSOMES AND RECOMBINANT UGT ENZYMES" PHARMACEUTICAL RESEARCH, NEW YORK, NY, US, vol. 19, no. 5, May 2002 (2002-05), pages 588-594, XP009019622 ISSN: 0724-8741 the whole document	1-20, 25-29
X	VOGEL A ET AL: "GENETIC LINK OF HEPATOCELLULAR CARCINOMA WITH POLYMORPHISMS OF THE UDP-GLUCURONOSYLTRANSFERASE UGT147 GENE" GASTROENTEROLOGY, W.B.SAUNDERS COMPANY, PHILADELPHIA, US, vol. 121, no. 5, November 2001 (2001-11), pages 1136-1144, XP001119046 ISSN: 0016-5085 the whole document	1-15,21, 22,25,26
X	US 2002/016293 A1 (RATAIN MARK J ET AL) 7 February 2002 (2002-02-07) paragraph '0070! - paragraph '0073!; claims 77-83	1-20, 25-29
X	GUILLEMETTE C ET AL: "STRUCTURAL HETEROGENEITY AT THE UDP-GLUCURONOSYLTRANSFERASE 1 LOCUS: FUNCTIONAL CONSEQUENCES OF THREE NOVEL MISSENSE MUTATIONS IN THE HUMAN UGT1A7 GENE" PHARMACOGENETICS, CHAPMAN & HALL, LONDON, GB, vol. 10, no. 7, October 2000 (2000-10), pages 629-644, XP009002994 ISSN: 0960-314X the whole document	1-15,21, 22,25,26
X	ANDO MAKI ET AL: "Genetic polymorphisms of the UDP-glucuronosyltransferase 1A7 gene and irinotecan toxicity in Japanese cancer patients." JAPANESE JOURNAL OF CANCER RESEARCH : GANN. MAY 2002, vol. 93, no. 5, May 2002 (2002-05), pages 591-597, XP002273391 ISSN: 0910-5050 the whole document	1-15,21, 22,25,26
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International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TUKEY R H ET AL: "HUMAN UDP-GLUCURONOSYLTRANSFERASES: METABOLISM, EXPRESSION, AND DISEASE" ANNUAL REVIEW OF PHARMACOLOGY AND TOXICOLOGY, ANNUAL REVIEW INC., PALO ALTO, CA, US, vol. 40, 2000, pages 581-616, 2 PAGES, XP009003008 ISSN: 0362-1642 the whole document	1-15, 23, 24
A	----- MACKENZIE PETER I: "Identification of uridine diphosphate glucuronosyltransferases involved in the metabolism and clearance of mycophenolic acid" THERAPEUTIC DRUG MONITORING, vol. 22, no. 1, February 2000 (2000-02), pages 10-13, XP009019790 ISSN: 0163-4356 the whole document	11
A	----- WOOLLEY ADAM T ET AL: "Direct haplotyping of kilobase-size DNA using carbon nanotube probes" NATURE BIOTECHNOLOGY, NATURE PUBLISHING, US, vol. 18, no. 7, July 2000 (2000-07), pages 760-763, XP002234415 ISSN: 1087-0156 the whole document	1-15, 21, 22, 25, 26

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6395481	B1	28-05-2002	US 2002115097 A1	22-08-2002
WO 0248400	A	20-06-2002	AU 2111202 A	24-06-2002
			EP 1352970 A1	15-10-2003
			WO 0248400 A1	20-06-2002
EP 1352970	A	15-10-2003	AU 2111202 A	24-06-2002
			EP 1352970 A1	15-10-2003
			WO 0248400 A1	20-06-2002
US 2002016293	A1	07-02-2002	AU 5361801 A	07-11-2001
			WO 0180896 A2	01-11-2001